Minimally invasive radio-guided surgery for primary hyperparathyroidism:
From preoperative to intraoperative localization imaging

Chirurgie mini-invasive de l’hyperparathyroïdie primaire par scintigraphie :
de l’imagerie préopératoire à intraopératoire

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Résumé

L’apparition et les progrès successifs de la parathyroïdectomie radioguidée mini-invasive (MIRP) ont révolutionné l’approche chirurgicale des adénomes parathyroïdiens. Le prérequis du succès est une localisation précise de la lésion en cause et dans ce but, une approche multimodale est couramment employée, associant imagerie anatomo- fonctionnelle. De toutes les techniques anatomo-physiques, l’échographie est la plus largement disponible mais demeure opérateur-dépendant et a une sensibilité réduite, spécialement en cas de nodules thyroïdiens. De même, la tomodensitométrie et l’imagerie par résonance magnétique nucléaire ont une sensibilité basse, tout en apportant des informations particulièrement intéressantes dans la détection des adénomes rétrotrachéaux, rétro-oesophagiens et médiastinaux. L’imagerie fonctionnelle par scintigraphie au Technetium-Sestamibi est actuellement l’examen le plus employé en sachant qu’il existe divers protocoles incluant une image en double contraste et un double isotope. La sensibilité et la spécificité sont améliorées par l’acquisition en tomographie par émission de photons simples (SPECT) et l’utilisation d’un scanner couplé avec un faible rayonnement pour fournir des images anatomiques (SPECT/CT). L’attitude actuellement recommandée est une combinaison d’imagerie fonctionnelle avec la scintigraphie au Technetium-Sestami et d’échographie de haute résolution complétée par une étude en sonde gamma peropératoire dans certains cas associée à la mesure rapide de la parathormone également peropératoire. Cette revue a pour but d’évaluer l’utilité des différentes modalités d’imagerie seules ou en combinaison dans l’exploration des adénomes parathyroïdiens et de faciliter une approche de parathyroïdectomie mini-invasive.

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Abstract

The introduction and successful implementation of minimally invasive radio-guided parathyroidectomy (MIRP) has revolutionized the surgical approach to remove parathyroid adenomas. A prerequisite for such success is an accurate localization of the offending adenoma. To achieve this goal, a multimodality approach is commonly employed using a combination of anatomical and functional imaging. Of the anatomical cross-sectional techniques, ultrasonography is the most widely available but is operator-dependent and has reduced sensitivity, specially in the presence of thyroid nodules. Similarly, computed tomography and magnetic resonance imaging have low sensitivities but provide value in detecting retrotracheal, retro-oesophageal and mediastinal adenomas. Functional imaging with 99mTc-Sestamibi is currently the most vital imaging procedure in this respect with variable protocols including dual-phase and dual isotope imaging. The sensitivity and specificity can improve by acquiring in single photon emission tomography (SPECT) mode and using co-registration with low dose CT to provide anatomical data (SPECT/CT). The current recommended approach is the combination of functional imaging with 99mTc-Sestamibi and high-resolution ultrasound (US), supplemented with intraoperative gamma probe in certain cases and quick persurgical measurement of parathyroid hormone. This review aims to explore the utility of various imaging modalities, alone and in combination, in detecting parathyroid adenoma and facilitating the current approach of MIRP.

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Keywords: Parathyroid adenoma; Minimally invasive parathyroidectomy; 99mTc-Sestamibi; Cross-sectional imaging

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Over the last 20 years, surgical approach to primary hyperparathyroidism (PHPT) has moved from bilateral neck exploration (BNE) to minimally invasive approaches, such as the minimally invasive radio-guided parathyroidectomy (MIRP) [1–2]. The development of MIRP was strictly related to the strong improvements in:

- preoperative localizing imaging, especially with $^{99m}$Tc-Sestamibi parathyroid scintigraphy;
- the intraoperative gamma probe;
- the measurement of intraoperative quick parathyroid hormone (QPTH) [2].

For the purpose of adopting MIRP in PHPT patients, the preoperative localizing imaging is mandatory to establish if the parathyroid adenoma (PA) is solitary, to precisely calculate the depth of the PA in the neck, to evaluate the presence of concomitant Sestamibi-avid thyroid nodules potentially causing intraoperative false positive results with the probe [3].

1. Anatomy and physiology

Parathyroid glands (PGs) derive from the third and fourth pharyngeal pouches and are generally four in number, subdivided in two upper and two lower glands. The upper PGs are located behind the superior third of the two thyroid lobes; the lower PGs are located behind the inferior third of the two thyroid lobes. The location of PGs, especially for the lower glands, is variable due to the longer pathway and more difficult migration process that they follow from their origin at the third pharyngeal pouch. Therefore, they can be intrathyroidal, within the thyrothymic ligament, within the thymus, in the mediastinum or fail to migrate and remain very high in the neck adjacent to the carotid sheath [1].

Although there are commonly four PGs, not infrequently, five or more PGs can be present. These supernumerary and accessory glands derive from the numerous dorsal and ventral wings of the pouches and can be variably located from the cricoid cartilage down into the mediastinum. The most probable location of accessory glands is in the thymic region [1,2].

The normal PGs are usually ovoid or bean-shaped but may be elongated, leaf-like or multilobulated. Their diameter is variable but should not be larger than 6–7 mm, and their individual weight ranges from 20 to 40 mg [1,2].

The PGs are composed of parenchymal and fat cells, the latter increasing with age. Among parenchymal cells, the chief cells produce the PTH, whereas the function of oxyphilic cells is unknown. However, oxyphilic cells are helpful in trapping the radiopharmaceuticals used in scintigraphy.

The main function of PTH is to regulate the blood calcium level: a decrease of blood calcium level, in particular the ionized form, stimulates PTH production and secretion. In fact, the surface membrane of parathyroid cells is equipped with a cation-sensitive receptor mechanism through which the cytosolic calcium concentration and PTH secretion are regulated [1–3].

PTH preserves the calcium, phosphate, and vitamin D homeostasis through several principal actions:

- stimulating renal tubular calcium reabsorption;
- stimulating urinary phosphate excretion through the inhibition of the sodium-phosphate cotransporter NPT2a;
- stimulating the activity of the 1alpha-hydroxylases and the synthesis of calcitriol;
- increasing calcium absorption from the gastrointestinal tract via the stimulation of calcitriol production;
- stimulating osteoclastic and osteoblastic activity in the bone (bone remodelling) that results in the release of calcium and phosphate from bone [1,2].

PHPT is characterized by increased production and secretion of PTH: it can be due to a hyperplastic or neoplastic disease of PGs, more frequently adenomas and most rarely carcinomas [1–3]. About 80% of PHPT is caused by a solitary adenoma (SA) [1–3]. This is a benign tumour that can vary in weight from less than 100 mg to more than 100 g (there is some correlation between size of adenoma and the degree of hypercalcaemia) [1–3]. Microscopically, the adenoma is surrounded by a rim of normal parathyroid tissue outside the capsule. It is formed predominantly of chief cells that are usually enlarged with nuclei larger and more variable in size compared to normal parathyroid tissue [1]. The nuclear pleomorphism is not a sign of malignancy but is considered a criterion to differentiate adenoma from hyperplasia. In patients with SA, the remainder PGs are generally smaller than normal glands and show signs of secretory inactivity on electron microscopy [1]. In about 5% of cases, typical adenomas affect more than one gland “double-adenomas” [2].

Parathyroid hyperplasia causes less than 15% of PHPT [1–3]. Chief cell hyperplasia is the most common type and it is characterized by a mixture of chief cells and to a lesser extent oxyphilic cells. The cells are arranged in a diffuse pattern or in nodules; sometimes, there is a mixture of both patterns. In PHPT, hyperplasia affects the glands asymptomatically, to varying degrees, and commonly one or two glands may be of normal size but show microscopic signs of endocrine hyperfunction [1–2].

Carcinoma of PGs represents less than 1% of cases of PHPT and can arise in any gland, usually in patients between the ages of 30 to 60 years and is generally accompanied by clinical signs of hyperparathyroidism. Unlike an adenoma, carcinoma is not encapsulated, is larger and appears lobulated, firm and often adherent to the surrounding structures [1].

PHPT can be sporadic or familial. The familial form can affect PGs exclusively or, more often, is part of a multiple endocrine neoplasia syndrome ( MEN). This is noted in MEN subtype 1 (MEN1), which is a combination of hyperparathyroidism, pituitary tumours and pancreatic neuroendocrine tumours, and MEN2a, characterized by hyperparathyroidism, medullary thyroid cancer and pheochromocytoma. In MEN1 and MEN2a, the disease usually involves more than one PG (parathyroid hyperplasia). It is worth noting that in case of recurrent hyperparathyroidism, a MEN syndrome must be suspected.

A rare association of hyperparathyroidism is the hyperparathyroidism–jaw tumour (HPT–JT) syndrome, a
familial cancer syndrome associated with renal and uterine tumours that can result from germline inactivation of \textit{HRPT2/CDC73}, a putative tumour suppressive gene that encodes parafibromin.

The consequent biochemical changes in PHPT are the result of a lack of calcium homeostasis: increased blood and urine calcium levels, decreased blood phosphate level and increased urinary phosphate level [1–3]. Clinically, this condition causes nephrocalcinosis, urolithiasis, bone disease, neuropsychiatric disorders (from mild behavioural changes to coma), gastrointestinal disturbances (from mild abdominal pain to acute pancreatitis) and neuromuscular manifestation (weakness, cramps and muscle pain) [2]. It is unusual for patients to present with florid symptoms due to increased use of laboratory tests encompassing routine chemistry screening. Most new cases of PHPT are indeed diagnosed in a subclinical state [4].

2. Preoperative localizing imaging: scintigraphy

2.1. Radiopharmaceuticals and scintigraphic techniques

The principal radiopharmaceuticals used for parathyroid imaging are 201Thallium, 99mTc-Sestamibi and 99mTc-Tetrofosmin [2]. Typically, there is no specific radiopharmaceutical that is trapped by PGs alone, so that subtraction of thyroid uptake by 99mTc-pertechnetate or 123Iodine imaging is necessary to visualize the enlarged PGs. Attempts have also been made with PET radiotracers, such as 11C-Methionine or 18F-Fluorodeoxyglucose, but only limited data have been published and the role of PET for the imaging of PGs remains to be established [5]. At the moment, due to its favorable physical and kinetic characteristics, 99mTc-Sestamibi is the most used radiopharmaceutical for parathyroid imaging in the clinical setting [3].

2.2. Dual-tracer subtraction technique

The peculiarity of Dual-tracer parathyroid scintigraphy is derived from the fact that a specific tracer for parathyroid tissue does not exist. In fact, the tracers utilized in routine parathyroid nuclear medicine imaging, like 201Thallium, 99mTc-Sestamibi or 99mTc-Tetrofosmin, are taken up not only by the hyperfunctioning PGs but also by thyroid tissue. It is therefore necessary to compare them with a second tracer that is specifically taken up by the thyroid gland, such as 99mTc-pertechnetate or 123Iodine. The distribution of the two tracers can be visually compared and, the thyroid uptake can be digitally subtracted from the parathyroid scan to remove the thyroid activity and enhance the visualization of the hyperfunctioning parathyroid tissue. Below are reported the principal dual-tracer subtraction techniques currently used in clinical practice.

2.2.1. Simultaneous dual-tracer 99mTc-Sestamibi and 123Iodine scanning

123Iodine is given intravenously. Two hours later, the patient is placed under the gamma camera and 99mTc-Sestamibi is injected. Images are acquired simultaneously using appropriate windows without energy overlap. Symmetric windows with 10% total width are one option (140 keV ± 5% and 159 keV ± 5%). Hindé et al. [6] used a 14% energy window centred over the 140 keV photopeak of 99mTc-Technetium, and an asymmetric window of 14% for 123Iodine (159 keV −4% +10%). This procedure increases count rates, while keeping cross-talk between isotopes to less than 5%, which does not require correction. Imaging can start three to five minutes after 99mTc-Sestamibi injection with a broad field of view of the neck and mediatinum extending from the submandibular salivary glands to the upper part of the myocardium to ensure detection of ectopic glands. Digital data are acquired in a 256 × 256 matrix using a low-energy, high-resolution, parallel-hole collimator (five minutes). A magnified image of the thyroid/parathyroid bed area is also obtained using a pinhole collimator (ten to 15 minutes).

2.2.2. Dual-tracer 99mTc-Pertechnetate and 99mTc-Sestamibi dual steps acquisition

99mTc-Pertechnetate/99mTc-Sestamibi introduced by Casara et al. [7]: patient is injected i.v. with 185 MBq 99mTc-Pertechnetate and after 20 minutes, the thyroid image is acquired. At the end, keeping the patient in the same position, 300 MBq of 99mTc-Sestamibi is administrated i.v. and a 20 minutes dynamic acquisition is performed. This protocol has good sensitivity and specificity but it has a drawback: high count rates from the thyroid gland do not allow, after subtraction, the identification of a small parathyroid hyperfunctioning gland located behind the thyroid [3,6].

99mTc-Pertechnetate/99mTc-Sestamibi modified by Geatti et al. [8]: this method uses reduced 99mTc-Pertechnetate activity and increased 99mTc-Sestamibi dose: 20 minutes after injection of 40–60 MBq of 99mTc-Pertechnetate, a ten-minute pinhole (or parallel-hole collimator) image of the neck is obtained. Then, without moving the patient, 600 MBq of 99mTc-Sestamibi is injected. Five minutes after injection, a pinhole image of the neck is recorded for 15 minutes (or a 20/35 minutes dynamic acquisition). 99mTc-Pertechnetate + Potassium perchlorate/99mTc-Sestamibi: this is a variant of the technique described above and was suggested by Rubello et al. [9]. This procedure consists of the administration \textit{per os} of 400 mg of potassium perchlorate immediately before starting acquisition of the thyroid scan, with the aim of inducing rapid 99mTc-Pertechnetate wash-out from the thyroid, therefore reducing its interference on the 99mTc-Sestamibi image. The doses are 150 MBq of 99mTc-Pertechnetate and 550–600 MBq of 99mTc-Sestamibi.

If imaging starts with a pinhole view over the thyroid, it is advised to leave a small safety margin above and below the visualized thyroid gland in order not to miss a parathyroid tumour slightly outside the thyroid bed area. A matrix size of 128 × 128 is adequate. A large field of view image with parallel-hole collimator is always necessary to detect ectopic parathyroids and should include the submandibular salivary glands and the upper part of the myocardium. A matrix size of 128 × 128 or 256 × 256 and a suitable zoom are recommended.
3. Dual-tracer subtraction scintigraphy single photon emission tomography

All the planar techniques described above can be associated with SPECT acquisition. Favorable results with 99mTc-Sestamibi planar and SPECT in PHPT have been reported by Rubello et al. particularly for PAs located deep in the neck or in ectopic sites [10]. The use of SPECT/CT has shown improved specificity and will be discussed in further details below.

3.1. Dual-phase or wash-out planar and single photon emission tomography scanning

Dual-phase parathyroid scintigraphy exploits the different wash-out timing that some radiotracers show in thyroid and parathyroid tissues: to find parathyroid hyperfunctioning tissue, wash-out timing of radiotracer from the parathyroid must be slower than from that of the thyroid tissue.

This type of parathyroid scintigraphy is a simplification of dual-tracer scan and was introduced by Taillfefer et al. [11] and refined in other centres [12].

For dual-phase parathyroid scintigraphy 99mTc-Sestamibi is the agent of choice with a recommended dose of 600–900 MBq (16–24 mCi) and is injected intravenously. Sestamibi is taken up by both normal thyroid tissue and hyperfunctioning PGs but the wash-out from normal thyroid tissue is faster.

99mTc-Tetrofosmin has a slower wash-out at the thyroid level, and effective differential wash-out does not exist. Based on evidence in the literature, it is suggested that the use of 99mTc-Tetrofosmin for dual-phase scintigraphy is not advised, and Sestamibi is the tracer of choice [6].

In some patients, especially in cases of nodular thyroid disease, after the dual-phase scan, a thyroid scan with 99mTc-Pertechnetate may be helpful to differentiate between thyroid nodules and pathological parathyroid tissue since a thyroid nodule can take up Sestamibi in a manner similar to hyperfunctioning PGs. This “hybrid technique” is recommended above all in endemic goiter areas. Before deciding to carry out the thyroid scan, it is necessary to be sure that the patient has no increased iodine saturation and is not receiving thyroid hormones, methimazole or propylthiouracil therapy. It is worth noting however that dual-phase scintigraphy with subsequent thyroid scan is less sensitive and specific than dual-tracer parathyroid scintigraphy [6].

Various acquisition protocols have been reported for dual-phase parathyroid scintigraphy in order to improve the image quality and accuracy of the technique. For this purpose, SPECT, SPECT/CT and pinhole/SPECT have been used and have the ability to more precisely locate the sites of the hyperfunctioning parathyroid than simple planar imaging and allow the detection of smaller lesions.

3.1.1. Planar technique

Digital data should be acquired in a 128 × 128 or larger matrix using a low-energy, high-resolution, parallel-hole collimator (pinhole or converging collimators, such as cone-beam, may increase count efficiency). A single-head gamma-camera can be used for planar images which must include anterior views of the neck and the upper thorax in all cases (oblique views are optional). The patient must be in the supine position with arms down. Early (ten to 15 minutes post-injection) and delayed (1.5–2.5 hours post-injection) high count images (at least 600 sec/image) are obtained. Further delayed images (four hours post-injection) can be obtained if thyroid wash-out is poor [11].

3.1.2. Single photon emission tomography technique

SPECT imaging has been shown to offer increased sensitivity and provide a more precise localization of abnormal PGs with a better anatomic demarcation of ectopic lesions [13]. SPECT study should be acquired immediately following early planar acquisitions (to avoid false negative results due to PAs with rapid wash-out) with the patient in the same position, using a matrix of 128 × 128 for 120 projections every 3° (360° rotation) and with an imaging time of 15–25 sec/projection and suitable zoom factor.

3.1.3. Single photon emission tomography/CT

Despite increasing sensitivity with SPECT, scintigraphic localization can be challenging without the thyroid gland as an anatomic landmark on early phase imaging and lack of other anatomic information. Co-registration of separately acquired Sestamibi SPECT and CT studies using external radiographic and scintigraphic markers has improved localization of ectopic PAs [14,15]. With the advent of hybrid SPECT/CT scanners, problematic misalignment between studies and cumbersome processing is avoided, thus aiding in precise localization of ectopic adenomas and facilitate surgery [16].

In a small retrospective study of 48 patients with PHPT undergoing Sestamibi scintigraphy with SPECT/CT [17], 32 patients had positive studies. SPECT/CT improved localization in four patients, and identified a false negative result thought to be positive on SPECT only. Localization by SPECT/CT was particularly useful in two cases of ectopic adenomas.

In another prospective study of 36 patients with PHPT, the use of SPECT/CT facilitated surgical exploration in the ten ectopic PAs identified but also in some (4/23) cervical adenomas by providing information on relationships to adjacent structures and organs. In a subgroup of patients awaiting re-exploration after failed initial surgery, SPECT/CT localization facilitated surgical resection [18].

A study comparing the use of Sestamibi SPECT/CT with dual isotope (123I/99mTc-Sestamibi) SPECT in 61 preoperative patients with PHPT, showed a significantly greater specificity of SPECT-CT (96 vs 48%) and more favorable receiver-operating–characteristic curves (ROC) when compared to SPECT only [19]. Improved specificity was afforded by SPECT/CT over SPECT primarily by the CT component allowing further characterization of SPECT findings, for example, in identification of artefactual activity or avid non-parathyroid lesions.

One recent study using dual-phase planar and delayed SPECT/CT imaging, as well as neck ultrasound (US), demonstrated 90% of solitary PAs detected by SPECT/CT. Adenomas...
Gamma probe effective in difficult intraoperative localization

4.1. Ultrasonography

The interpretation of scintigraphy and US, or scintigraphy and CT, has a great impact on diagnosis in oncology. Combined methods, such as SPECT/CT and PET/CT and combined intercalary importance. Correlative metabolic imaging with anatomic localization of ectopic mediastinal lesions for surgical planning. Evaluation of patients with combined modalities is gaining clinical importance. Correlative metabolic imaging with anatomic methods, such as SPECT/CT and PET/CT and combined interpretation, has a great impact on diagnosis in oncology. Combined interpretation of scintigraphy and US, or scintigraphy and CT, can improve the diagnostic interpretation of parathyroid scintigraphy and clinical decision-making.

4.1.1. Ultrasonography

US is widely available and largely used for the purpose of localizing PAs. However, it has some limitations mainly due to its highly operator-dependant nature and subjectivity in interpretation. Solitary PA usually present on US as a homogeneous well demarcated ovoid hypoechoic nodule. Inferior PAs are usually located close to the inferior pole of the thyroid lobes, but they could also be located near or beyond the jugular-carotid axis or the thyrothymic ligament or in the upper, middle or lower portion of the thymus. Superior PAs are usually located close to the posterior border of the thyroid lobe and tend to migrate posteriorly and in a downward direction assuming a pear-shaped aspect.

Several studies have shown a lower sensitivity and accuracy of US compared with scintigraphy for showing PGs. However, when US is used together with scintigraphy, it can provide important information for the diagnosis of parathyroid diseases. US is useful to differentiate PGs from thyroid nodules. US-guided aspiration biopsy is also suggested for the differential diagnosis of intrathyroidal PA from a thyroid nodule. The pitfalls of US in which it has lower success rates include intrathyroidal PGs and especially mediastinal parathyroid lesions, where it has no practical use.

4.2. Computed tomography and magnetic resonance

Despite CT being a more successful imaging modality than US for retrotracheal, retro-oesophageal and mediastinal adenomas, its sensitivity is very low for ectopic lesions located in the lower neck at the level of shoulders and lesions close to or within thyroid gland. MR is more commonly used for mediastinal ectopic PGs.

5. Minimally invasive radio-guided parathyroidectomy

Although traditional BNE is characterized by a high cure-rate for PHPT patients in the hands of skilled endocrine surgeons, minimally invasive approach has been developed in many centres due to some advantages over BNE, such as:

- the favorable cosmetic results;
- the reduction in the duration of intervention and hospital stay;
- the possibility to perform the operation under local anesthesia;
- the lower costs.

With the aim of limiting the operative field, in the early 1980s, Tibblin et al. [25] proposed a procedure based on unilateral
neck exploration with the removal of the PA and the biopsy of the ipsilateral PG to exclude concomitant glandular hyperplasia. More recently, minimally invasive endoscopic [26] and MIRP [10,24,27,28] approaches were developed.

The success of MIRP has been particularly favoured by the improvements achieved in preoperative localization imaging, especially with $^{99m}$Tc-Sestamibi scintigraphy [2,6–23].

As regards to $^{99m}$Tc-Sestamibi scintigraphy role, and at variance with BNE, MIRP requires stringent inclusion criteria:

- a high likelihood of a solitary PA demonstrated at preoperative $^{99m}$Tc-Sestamibi scintigraphy;
- a clear $^{99m}$Tc-Sestamibi uptake in the PA;
- the absence of concomitant Sestamibi-avid thyroid nodules.

Adopting these selection criteria, approximately 50 to 70% of all PHPT patients can be offered MIRP as an alternative to BNE [2,6,24,27,28].

5.1. Gamma probe

The gamma detecting intraoperative probe is a hand-held radiation detector device which gives both auditory signals and digital counts to guide the surgeon to dissect the radioactive target tissue. From a technical point of view, some aspects of the physical characteristics of the probes used for radio-guided parathyroidectomy need to be pointed out:

- for the purpose of a minimally invasive surgery, it is obviously recommended to use the smallest sized probe, that is the 11 mm diameter;
- other probes, such as the 14–15 mm diameter, can be useful in cases of only a mild uptake of $^{99m}$Tc-Sestamibi in PA in which a higher sensitivity is advisable.

As regard to commercially available probes, scintillation probes seem to provide better sensitivity in comparison with the semi-conductor probes, but the latter have higher spatial resolution. Despite these considerations, no significant differences between the two types of probes have been reported in clinical practice. Instead, a very important point for the purpose of a parathyroid radio-guided surgery is that a well “collimated” probe is mandatory, mainly because the background activity (i.e. thyroid gland) is significantly higher in parathyroid surgery in respect to other types of radio-guided surgery, such as the axillary sentinel node biopsy [29].

5.2. Minimally invasive radio-guided parathyroidectomy protocols

The first MIRP protocol was developed by Norman and Chheda in 1997 [27]. It consists of a single-day, imaging and surgery approach; the patient is injected with a 740–925 MBq $^{99m}$Tc-Sestamibi activity and images are obtained by dual-phase technique and MIRP is performed within two to three hours from radiopharmaceutical administration. Norman’s protocol is attractive from a cost-analysis perspective because $^{99m}$Tc-Sestamibi scintigraphy and MIRP are performed on the same day and a single $^{99m}$Tc-Sestamibi dose is used both for preoperative imaging and radio-guided surgery. However, it presents some practical disadvantages, given the uncertainty of the scintigraphic results and the differences between the MIRP and BNE with respect to the need for operating suite time (BNE time is approximately double that of MIRP) and efficient patient scheduling. This problem would be expected to be even more relevant in geographic areas with high prevalence of nodular goiter so that a different-day protocol would be preferable [2,6].

Murphy andorman [30] found also that any excised tissue containing more than 20% of background radioactivity at the operative basin was consistent with hyperfunctioning parathyroid tissue. This method is called the “20% rule” and implicates that measurement of the radioactivity in the excised tissue allows the physician to distinguish hyperfunctioning parathyroid tissue from normal parathyroid tissue and other neck structures in order to make the appropriate operative decisions and avoiding unnecessary frozen section analysis and the measurement of quick PTH.

The protocol of Pelizzo and Rubello [28] is a different-day protocol: in the first day, a double-tracer $^{99m}$Tc-Pertecnetate/$^{99m}$Tc-Sestamibi subtraction scintigraphy is obtained. On the day of MIRP (within one week from imaging), a low 37 MBq activity of $^{99m}$Tc-Sestamibi is given to the patient directly in the operating suite few minutes before surgery. The ‘low Sestamibi dose protocol’ provides two main advantages: less radiation exposure to the patient and operating theatre personnel and avoids false negative results in PA with rapid $^{99m}$Tc-Sestamibi wash-out [31]. Unfortunately, using the “low 37 MBq $^{99m}$Tc-Sestamibi dose” protocol and the ‘20% rule’ of Norman does not work, because it is not able to distinguish abnormal PGs from normal thyroid tissue. The explanation of this discrepancy may be related to the different kinetic conditions and tissue concentrations of $^{99m}$Tc-Sestamibi with the two different protocols (the probe counting is performed two to three hours post-injection with the Norman protocol and ten to 20 minutes post-injection with the Pelizzo and Rubello protocol) [32]. As a consequence, using the Pelizzo and Rubello ‘low 37 MBq $^{99m}$Tc-Sestamibi dose’ protocol requires the performance of quick PTH levels intraoperatively as an important step for the purpose of evaluating the effectiveness of detection [32].

Both with Norman protocol [27] and Pelizzo and Rubello protocol [28], the probe-guided surgery allows:

- to intraoperatively rapidly detect the PA, this is particularly useful for PA located deep in the neck or in ectopic sites;
- to facilitate surgery and minimize complications during neck reoperation;
- to verify the effectiveness of complete parathyroid tissue removal checking the empty parathyroid bed after the operation;
- to look for residual activity in other sites in the neck when there is suspicion of a second PA or glandular hyperplasia;
to verify the removal of a $^{99m}$Tc-Sestamibi-avid PA by checking the removed surgical specimen ex vivo.

Both a middle (cut incision performed approximately 1 cm above the sternal notch) or a lateral 2 cm access are currently used with MIRP in surgical practice. The later access is preferred in superior PGs while the middle access for the inferior PGs and in case the surgeon would need to convert the operation to a BNE.

Favorable results have been reported with both Norman ‘high 740 MBq $^{99m}$Tc-Sestamibi dose protocol’ and Pelizzo and Rubello ‘low 37 MBq Sestamibi dose protocol’ with a success rate in the intraoperative detection of PA higher than 90%, without major intraoperative surgical complications [27,28]. Moreover, long-term results are also favorable as demonstrated in the present study. It appears reasonable to think that the Norman single-day protocol could be preferable in patients with a low-likelihood of nodular goiter disease, while our different-day protocol should be preferred in geographic areas with a high prevalence of nodular goiter [6].

5.3. Radiation safety

In order to decrease the radiation dose to operating room personnel, the lowest dose of $^{99m}$Tc-Sestamibi that is necessary to effectively locate the pathologic parathyroid tissue should be given. Surgeons and operating room personnel are considered non-radiation workers and are allowed 1 mSv annual dose limit. Norman and Chheda calculated 0.05 mSv per patient to the surgeons and Chheda calculated 0.05 mSv per patient to the norman single-day protocol could be preferable in patients with a low-likelihood of nodular goiter disease, while our different-day protocol should be preferred in geographic areas with a high prevalence of nodular goiter [6].

In conclusion, MIRP has proven to be a safe and effective therapeutic approach for PHPT patients with a high preoperative probability of being affected by a solitary PA. In this view, an accurate preoperative imaging based on $^{99m}$Tc-Sestamibi scintigraphy is mandatory.

Conflict of interest

The authors declare any conflict of interest with the present paper.

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